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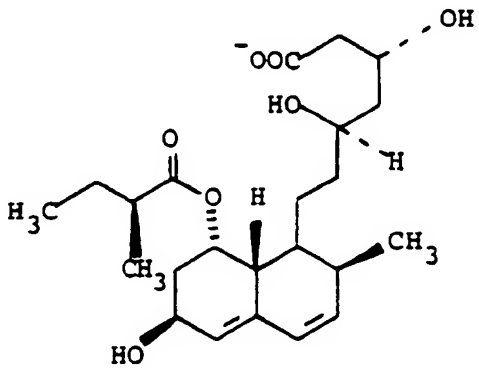
Description

The present invention relates to a pharmaceutical composition, preferably in the form of a tablet, which includes pravastatin, which is sensitive to a low pH environment, yet has excellent stability.

Pharmaceutical compositions which include a medicament which is unstable in an acidic environment will require a basic excipient to enhance storage stability.

Pravastatin, an HMG-CoA reductase inhibitor disclosed in U.S. Patent No. 4,346,227 having the formula



is sensitive to a low pH environment and will degrade to form its lactone and various isomers.

In accordance with the present invention, a pharmaceutical composition is provided which has excellent storage stability even though it includes a medicament which may degrade in a low pH environment. The pharmaceutical composition of the invention, which is preferably in the form of a tablet, includes pravastatin which is sensitive to a low pH environment, one or more fillers, such as lactose and/or microcrystalline cellulose, one or more binders, such as mirocrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate, and one or more basifying agents such as magnesium oxide to impart a pH to an aqueous dispersion of the composition of at least 9.0. Pravastatin, will be present in an amount of 1 to 60% and preferably from 3 to 50% by weight of the composition.

To ensure acceptable stability, the composition of the invention will include a basifying agent which will raise the pH of an aqueous dispersion of the composition to at least 9 and preferably to a pH of at least 9.5. The basifying agent will be present in an amount from 1 to 75% by weight and preferably from 2 to 70% by weight of the composition. Examples of basifying agents which may be included herein include magnesium oxide, aluminum oxide, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide or an alkaline earth metal hydroxide such as calcium hydroxide or magnesium hydroxide, or magaldrate with magnesium oxide being preferred.

The composition of the invention will also include one or more fillers or excipients in an amount of 5 to 90% by weight and preferably from 10 to 80% by weight such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium carbonate and/or cellulose derivatives such as wood cellulose and microcrystalline cellulose.

One or more binders will be present in addition to or in lieu of the fillers in an amount of 5 to 35% and preferably from 10 to 30% by weight of the composition. Examples of such binders which are suitable for use herein include polyvinylpyrrolidone (molecular weight ranging from 5000 to 80,000 and preferably 40,000), lactose, starches such as corn starch, modified corn starch, sugars, and gum acacia as well as a wax binder in finely powdered form (less than 500 μm (microns) such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

Where the composition is to be in the form of a tablet, it will include one or more tablet disintegrants in an amount from 0.5 to 10% and preferably from 2 to 8% by weight of the composition such as croscarmellose sodium, crospovidone, sodium starch glycolate, corn starch or microcrystalline cellulose as well as one or more tabletting lubricants in an amount of 0.2 to 8% and preferably from 0.5 to 2% by weight of the composition, such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, and carnauba wax. Other conventional ingredients which may optionally be present include preservatives, stabilizers, anti-adherents or silica flow conditioners or glidants, such as Syloid brand silicon dioxide as well as FD&C colors.

Tablets of the invention may also include a coating layer which may comprise from 0 to 15% by weight of the tablet composition. The coating layer which is applied over the tablet core may comprise any conventional

coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethyl cellulose and a hydrophobic polymer like ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, β-pinene polymers and glyceryl esters of wood resins and one or more plasticizers, such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthlate, and castor oil. Both core tablets as well as coating formulations may contain aluminum lakes to provide color.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols like methyl alcohol, ethyl alcohol or isopropyl alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

Where a color is employed, the color will be applied together with the film former, plasticizer and solvent compositions.

A preferred tablet composition of the invention will include from 2 to 35% by weight pravastatin, from 2.5 to 70% by weight magnesium oxide, from 10 to 80% by weight lactose, from 10 to 30% by weight microcrystalline cellulose or polyvinylpyrrolidone, from 2 to 8% by weight croscarmellose sodium and from 0.5 to 2% by weight magnesium stearate.

The pharmaceutical composition of the invention may be prepared as follows. A mixture of prevastatin, basifying agent (preferably magnesium oxide), and a fraction (less than 50%) of the filler (such as lactose) with or without color, are mixed together and passed through a #12 to #40 mesh screen. Filler-binder (such as microcrystalline cellulose) disintegrant (such as croscarmellose sodium) and the remaining lactose are added and mixed. Lubricant (such as magnesium stearate) is added with mixing until a homogeneous mixture is obtained. The resulting mixture may then be compressed into tablets of up to 1 in weight.

Where desired, the tablets of the invention may be formulated by a wet granulation technique wherein pravastatin is dissolved in warm aqueous solution of binder (polyvinylpyrrolidone). The resulting solution is used to granulate a mixture of filler (lactose hydrous), basifying agent (such as magnesium oxide), filler-binder (microcrystalline cellulose), and a portion of the disintegrant (croscarmellose sodium). The granulated mixture is passed through a #4 to #10 mesh screen and is then dried in a tray drying oven. The dried granulation is passed through a #12 to #20 mesh screen. The remainder of the disintegrant and the lubricant (such as magnesium stearate) are added and the resulting granules are compressed into a tablet.

The tablets may also be formulated by a wet granulation technique where a mixture of pravastatin, basifying agent (preferably magnesium oxide), filler-binder (such as microcrystalline cellulose), and a fraction (less than 50%) of the filler (such as lactose) with or without color, are mixed and passed through a #12 to #40 mesh screen. A portion of the disintegrant (such as croscarmellose sodium) and the remaining lactose are added and mixed. The resulting mixture is granulated using an aqueous binder solution (such as polyvinyl pyrrolidone). The formulated wet mixture is passed through a #4 to #20 mesh screen and is then dried in a tray drying oven. The dry granulation is passed through a #12 to #20 mesh screen. The remainder of the disintegrant and the lubricant (such as magnesium stearate) are added and the resulting granules are compressed into a tablet.

All mesh sizes are U.S. Standard ASTME.

The following Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated and all mesh sizes are U.S. Standard ASTME.

Example 1

A pravastatin formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Percent by Weight
Pravastatin	6.7
Lactose	67
Microcrystalline cellulose	20
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3

Pravastatin, magnesium oxide and a fraction (30%) of the lactose were mixed together for 2 to 10 minutes employing a suitable mixer. The resulting mixture was passed through a #12 to #40 mesh size screen. Micro-

crystalline cellulose, croscarmellose sodium and the remaining lactose were added and the mixture was mixed for 2 to 10 minutes. Thereafter, magnesium stearate was added and mixing was continued for 1 to 3 minutes.

The resulting homogeneous mixture was then compressed into tablets each containing 5 mg, 10 mg, 20 to 40 mg pravastatin.

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C, or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 2

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg or 40 mg pravastatin, having the following composition was prepared as described in Example 1, except that color was incorporated into the powder mixture containing pravastatin, magnesium oxide and a fraction of the lactose.

Ingredient	Percent by Weight
Pravastatin	6.7
Lactose	66.8
Microcrystalline cellulose	20
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3
FD&C Red #3 Lake	0.2

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C, or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 3

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg or 40 mg pravastatin, having the following composition was prepared as described below.

Ingredient	Percent by Weight
Pravastatin	6.7
Lactose	71
Microcrystalline cellulose	15
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3
Polyvinylpyrrolidone	1

Pravastatin was dissolved in warm aqueous solution of polyvinylpyrrolidone. The solution was used to granulate a mixture of lactose, magnesium oxide, microcrystalline cellulose and a fraction of the croscarmellose sodium. The formulated mixture was passed through a #4 to #10 mesh screen and was then dry granulated in a tray drying oven. The dry granulation was passed through a #12 to #20 mesh screen. The remainder of the disintegrant was added to the dry granules and mixed for 2 to 10 minutes. Thereafter, magnesium stearate was added and mixing was continued for 1 to 5 minutes. The resulting granulation was compressed into tablets.

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 4

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg or 40 mg pravastatin, having the following composition was prepared as described in Example 3, except that color was incorporated into the powder mixture containing lactose, magnesium oxide, microcrystalline cellulose and a fraction of the croscarmellose sodium

Ingredient	Percent by Weight
Pravastatin	6.7
Lactose	70.8
Microcrystalline cellulose	15
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3
FD&C #3 Lake	0.2
Polyvinylpyrrolidone	1

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 5

A pravastatin formulation in the form of tablets, each containing 10 mg pravastatin, having the following composition was prepared as described in Example 3.

Ingredient	Percent by Weight
Pravastatin	6.7
Lactose	54.5
Polyvinylpyrrolidone	0.5
Croscarmellose sodium	4
Magnesium stearate	1
Magnesium oxide	33.3

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 40°C for 18 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 6

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg and 40 mg pravastatin, having the following composition was prepared as described below.

Ingredient	Percent by Weight
Pravastatin	10
Lactose	66.7
Microcrystalline cellulose	15
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3
Polyvinylpyrrolidone	2

Pravastatin, magnesium oxide, microcrystalline cellulose, and a fraction of the lactose were mixed for 5-10 minutes. The resulting mixture was passed through a #12 to #40 mesh screen. A portion of the croscarmellose sodium and the remaining lactose were added and mixing was continued for 5-10 minutes. The resulting mixture was granulated with an aqueous polyvinylpyrrolidone solution. The granulated wet mixture was passed through a #4 to #20 mesh screen and then dried in a tray drying oven. The dry granulation was passed through a #12-#20 mesh screen. The remainder of the croscarmellose sodium was added to the granules and mixed for 5-10 minutes. The magnesium stearate was added to the resulting granule mixture and mixing was continued for 1-5 minutes. The resulting formulation was compressed into tablets.

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 7

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg and 40 mg pravastatin, having the following composition was prepared as described in Example 6, except that FD&C Red #3 Lake color was mixed with pravastatin, magnesium oxide, microcrystalline cellulose and lactose.

Ingredient	Percent by Weight
Pravastatin	10
Lactose	66.5
Microcrystalline cellulose	15
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3.3
FD&C Red #3 Lake	0.2
Polyvinylpyrrolidone	2

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 8

A pravastatin formulation in the form of tablets, each containing 5 mg, 10 mg, 20 mg and 40 mg pravastatin, having the following composition was prepared as described in Example 6, except that all of the croscarmellose sodium was mixed with dry granules prior to addition of magnesium stearate.

Ingredient	Percent by Weight
Pravastatin	10
Lactose	64.7
Microcrystalline cellulose	15
Croscarmellose sodium	5
Magnesium stearate	1
Magnesium oxide	3.3
Polyvinylpyrrolidone	1

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 60°C or 40°C/75% relative humidity for 2 months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Example 9

A pravastatin formulation in the form of tablets, having the following composition was prepared as described in Example 8 except that FD&C Red #3 Lake color was mixed with pravastatin, magnesium oxide, microcrystalline cellulose and lactose.

Ingredient	Percent by Weight
Pravastatin	10
Lactose hydrous	64.5
Microcrystalline cellulose	15
Polyvinylpyrrolidone	1
Croscarmellose sodium	5
Magnesium stearate	1
Magnesium oxide	3.3
FD&C #3 Lake	0.2

A dispersion of the tablets in water had a pH of about 10.

Upon subjecting the so-formed tablets to a stability study at 40 to 60°C for several months, it was found that the tablets including the pravastatin remained substantially stable; no lactone formation was observed.

Other basifying agents may be employed which will raise the pH of an aqueous dispersion of the composition of the invention as shown in Examples 1 to 9 to about 10. Examples of such basifying agents include NaOH, KOH, $Ca(OH)_2$, $Mg(OH)_2$ or NH_4OH.

Claims

1. A pharmaceutical composition which has enhanced stability comprising pravastatin, one or more fillers, one or more binders, one or more disintegrants, one or more lubricants and one or more basifying agents to impart a desired pH of at least 9 to an aqueous dispersion of said composition.

2. The pharmaceutical composition as defined in Claim 1 wherein pravastatin is present in an amount of 1 to 60% by weight of the composition.

3. The pharmaceutical composition as defined in Claim 1 wherein the basifying agent is present in an amount of 1 to 75% by weight of the composition.

4. The pharmaceutical composition as defined in Claim 1 wherein the basifying agent is an alkali metal

hydroxide, an alkaline earth metal hydroxide or ammonium hydroxide.

5. The pharmaceutical composition as defined in Claim 4 wherein the basifying agent is MgO, $Mg(OH)_2$, $Ca(OH)_2$, NaOH, KOH, LiOH, NH_4OH, $Al(OH)_3$ or magaldrate.

6. The pharmaceutical composition as defined in Claim 1 wherein the filler is present in an amount of 5 to 90% by weight.

7. The pharmaceutical composition as defined in Claim 6 wherein the filler is lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, wood cellulose, microcrystalline cellulose, calcium carbonate or mixtures thereof.

8. The pharmaceutical composition as defined in Claim 1 wherein the binder is present in an amount of 5 to 35% by weight.

9. The pharmaceutical composition as defined in Claim 8 wherein the binder is microcrystalline cellulose, polyvinylpyrrolidone, lactose, corn starch, modified corn starch, sugars, gum acacia, carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

10. The pharmaceutical composition as defined in Claim 1 wherein the disintegrant is present in an amount of 0.5 to 10% by weight.

11. The pharmaceutical composition as defined in Claim 10 wherein the disintegrant is croscarmellose sodium crospovidone, sodium starch glycolate, corn starch or microcrystalline cellulose.

12. The pharmaceutical composition as defined in Claim 1 having the following formulation:
from 3 to 50% by weight pravastatin,
from 2 to 70% by weight magnesium oxide, to impart a pH of at least 9.5,
from 1 to 85% by weight lactose,
from 10 to 30% by weight microcrystalline cellulose or polyvinylpyrrolidone,
from 2 to 8% by weight of croscarmellose sodium; and
from 0.5 to 2% by weight magnesium stearate.

13. The pharmaceutical composition as defined in Claim 1 having a pH in water of 10.

Patentansprüche

1. Arzneimittel mit erhöhter Stabilität, umfassend Pravastatin, einen oder mehrere Füllstoffe, ein oder mehrere Bindemittel, ein oder mehrere Sprengmittel, ein oder mehrere Gleitmittel und ein oder mehrere Alkalisierungsmittel, um einer wäßrigen Dispersion der Zusammensetzung einen gewünschten pH-Wert von mindestens 9 zu verleihen.

2. Arzneimittel nach Anspruch 1, in dem Pravastatin in einer Menge von 1 bis 60 Gewichtsprozent der Zusammensetzung vorliegt.

3. Arzneimittel nach Anspruch 1, in dem das Alkalisierungsmittel in einer Menge von 1 bis 75 Gewichtsprozent der Zusammensetzung vorliegt.

4. Arzneimittel nach Anspruch 1, in dem das Alkalisierungsmittel ein Alkalimetallhydroxid, ein Erdalkalimetallhydroxid oder Ammoniumhydroxid ist.

5. Arzneimittel nach Anspruch 4, in dem das Alkalisierungsmittel MgO, $Mg(OH)_2$, $Ca(OH)_2$, NaOH, KOH, LiOH, NH_4OH, $Al(OH)_3$ oder Magnesiumaluminiumhydrat ist.

6. Arzneimittel nach Anspruch 1, in dem der Füllstoff in einer Menge von 5 bis 90 Gewichtsprozent vorliegt.

7. Arzneimittel nach Anspruch 6, in dem der Füllstoff Lactose , Zucker, Maisstärke, modifizierte Maisstärke, Mannitol, Sorbitol, Holzcellulose, mikrokristalline Cellulose, Calciumcarbonat oder Gemische davon ist.

8. Arzneimittel nach Anspruch 1, in dem das Bindemittel in einer Menge von 5 bis 35 Gewichtsprozent vorliegt.

9. Arzneimittel nach Anspruch 8, in dem das Bindemittel mikrokristalline Cellulose, Polyvinylpyrrolidon, Lactose, Maisstärke, modifizierte Maisstärke, Zucker, Gummi arabicum, Karnaubawachs, Paraffin, Walrat, Polyethylene oder mikrokristallines Wachs ist.

10. Arzneimittel nach Anspruch 1, in dem das Sprengmittel in einer Menge von 0,5 bis 10 Gewichtsprozent vorliegt.

11. Arzneimittel nach Anspruch 10, in dem das Sprengmittel Natriumcroscarmellose, Crospovidon, Natriumstärkeglykolat, Maisstärke oder mikrokristalline Cellulose ist.

12. Arzneimittel nach Anspruch 1 mit der folgenden Formulierung:
3 bis 50 Gewichtsprozent Pravastatin,
2 bis 70 Gewichtsprozent Magnesiumoxid, um einen pH-Wert von mindestens 9,5 zu erreichen,
1 bis 85 Gewichtsprozent Lactose,
10 bis 30 Gewichtsprozent mikrokristalline Cellulose oder Polyvinylpyrrolidon,

2 bis 8 Gewichtsprozent Natriumcroscarmellose; und
0,5 bis 2 Gewichtsprozent Magnesiumstearat.

13. Arzneimittel nach Anspruch 1 mit einem pH-Wert von 10 in Wasser.

Revendications

1. Composition pharmaceutique possédant une stabilité accrue, comprenant de la pravastatine, une ou plusieurs charges, un ou plusieurs liants, un ou plusieurs agents de désintégration, un ou plusieurs lubrifiants, et un ou plusieurs alcalinisants servant à donner un pH voulu, au moins égal à 9, à une dispersion aqueuse de ladite composition.

2. Composition pharmaceutique selon la revendication 1, dans laquelle la pravastatine représente de 1 à 60% du poids de la composition.

3. Composition pharmaceutique selon la revendication 1, dans laquelle l'alcalinisant représente de 1 à 75% du poids de la composition.

4. Composition pharmaceutique selon la revendication 1, dans laquelle l'alcalinisant est un hydroxyde de métal alcalin, un hydroxyde de métal alcalino-terreux ou l'hydroxyde d'ammonium.

5. Composition pharmaceutique selon la revendication 4, dans laquelle l'alcalinisant est MgO, $Mg(OH)_2$, $Ca(OH)_2$, NaOH, KOH, LiOH, NH_4OH, $Al(OH)_3$ ou le magaldrate.

6. Composition pharmaceutique selon la revendication 1, dans laquelle la charge représente de 5 à 90% du poids de la composition.

7. Composition pharmaceutique selon la revendication 6, dans laquelle la charge est constituée par du lactose, du sucre, de l'amidon de maïs, de l'amidon de maïs modifié, du mannitol, du sorbitol, de la cellulose de bois, de la cellulose microcristalline, du carbonate de calcium, ou un mélange de ceux-ci.

8. Composition pharmaceutique selon la revendication 1, dans laquelle le liant représente de 5 à 35% du poids de la composition.

9. Composition pharmaceutique selon la revendication 8, dans laquelle le liant est constitué par de la cellulose microcristalline, de la polyvinylpyrrolidone, du lactose, de l'amidon de maïs, de l'amidon de maïs modifié, des sucres, de la gomme arabique, de la cire de carnauba, de la paraffine, du spermaceti, un polyéthylène ou une cire microcristalline.

10. Composition pharmaceutique selon la revendication 1, dans laquelle l'agent de désintégration représente de 0,5 à 10% du poids de la composition.

11. Composition pharmaceutique selon la revendication 10, dans laquelle l'agent de désintégration est constitué par de la croscarmellose sodique, de la crospovidone, du glycolate d'amidon sodique, de l'amidon de maïs, ou de la cellulose microcristalline.

12. Composition pharmaceutique selon la revendication 1, ayant la formule suivante:
de 3 à 50% en poids de pravastatine,
de 2 à 70% en poids d'oxyde de magnésium, pour donner un pH au moins égal à 9,5,
de 1 à 85% en poids de lactose,
de 10 à 30% en poids de cellulose microcristalline ou de polyvinylpyrrolidone,
de 2 à 8% en poids de croscarmellose sodique, et
de 0,5 à 2% en poids de stéarate de magnésium.

13. Composition pharmaceutique selon la revendication 1, ayant dans l'eau un pH de 10.